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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 05/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,647	IKEDA ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-10* is/are rejected.

7)☒ Claim(s) *7 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed March 8, 2004. Claims 1-10 were previously pending. Applicants amended claims 1, 5 and 6, and cancelled claims 3 and 4. Claims 1, 2 and 5-10 are pending and will be examined.

2. Applicants' amendments and claim cancellations obviated the following rejections: rejection of claims 2 and 3 under 35 U.S.C. 112, first paragraph, enablement; rejection of claims 1, 2 and 7-10 under 35 U.S.C. 102(b) over Baumann et al.; rejection of claims 2 and 3 under 35 U.S.C. 102(a) over Ikeda et al.

3. The declarations under 37 CFR 1.132 filed March 8, 2004, regarding authorship of the Ikeda et al. paper, are sufficient to overcome the rejection of claims 1, 2 and 5-10 based upon the Ikeda et al. reference.

4. The declaration under 37 CFR 1.132 filed March 8, 2004, regarding polymorphisms in the untranslated region of the μ-opioid receptor of human subjects, is insufficient to overcome the rejection of claims 1, 2 and 5-10 under 35 U.S.C. 112, first paragraph, enablement, as set forth in the last Office action because: Applicants did not show that the presence of the 56 polymorphisms in human subjects resulted in altered sensitivity to any of the drugs which target the the μ-opioid receptor. Claim 1 is structured in such a way that the presence of the differences in the untranslated regions requires correlation with altered sensitivity to the drugs. The rejection is restated in view of Applicants' amendments, and the response to Applicants' arguments is provided below.

Response to Arguments

5. Applicant's arguments filed March 8, 2004 have been fully considered but they are not persuasive.

Regarding the rejection of claims 1, 2, 3, 4 and 7-10 under 35 U.S.C. 112, first paragraph, enablement, Applicants argue that the declaration under 37 CFR 1.132, showing that humans also have polymorphisms in the UTR of the μ-opioid receptor gene, provides enablement for claim 1 with respect to humans. However, the only polymorphism which affected drug sensitivity in mice was a difference in the length of the UTR region. Applicants did not provide any evidence that any of the 56 polymorphisms discovered in humans resulted in altered drug sensitivity with respect to drugs targeting the μ-opioid receptor, and claim 1 requires that the presence of the differences in the untranslated regions requires correlation with altered sensitivity to the drugs.

The rejection is maintained.

Claim Objections

6. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 is drawn to a method in which drugs which target the μ-opioid receptor are used, whereas claim 7 lists drug categories such as carcinostatics, anti-allergy agents, hypotensors, diuretics and anesthetics, which do not target the μ-opioid receptor.

7. Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 is drawn to a method of detecting a difference in the untranslated region of the μ-opioid receptor gene, whereas claim 9 is drawn to genes of drug receptors, or genes involved in metabolism of drugs.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for evaluating sensitivity of mice to morphine and (-) U-50488 based on the length of the untranslated region of the μ-opioid receptor gene, does not reasonably provide enablement for evaluating sensitivity to any other drug targeting the μ-opioid receptor in other animals or humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are broadly drawn to a method for evaluating sensitivity of a human or animal to any drug targeting the μ-opioid receptor based on detecting a difference in an untranslated region of mRNA for a μ-opioid receptor gene in which diversity in the untranslated region affects the

sensitivity to a drug, and evaluating the sensitivity to a drug based on the detected difference. However, as will be further discussed, there is no support in the specification and prior art for the method in any animal other than mouse, and only for morphine and (-) U-50488. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification.

The specification provides no evidence that the disclosed effect of length change in the UTR region of the mouse μ-opioid receptor gene resulting in the altered sensitivity to morphine would have similar effect in other animals or humans. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. Applicants describe two possible scenarios of discovering drug sensitivity of animals or humans, based either on PCR amplification or microarray hybridization of mRNA (page 4, 5). However, these are very general methods which do not provide guidance of how to determine, for example, which one(s) of the genes might be involved in metabolism of a certain drug.

The presence or absence of working examples

Applicants investigated the genetic basis of morphine sensitivity in CXBK mice, which show reduced analgesic effect of morphine. The specification describes detection of a difference in length of the 5' UTR region of the mouse μ-opioid receptor gene and determination of sensitivity to morphine and (-) U-50488 in mice homozygous and heterozygous for the altered μ-opioid receptor gene (Example 1 (1), (3) and (5)). However, no examples were provided showing that altered length of the 5' UTR region of the μ-opioid receptor gene would alter morphine sensitivity in any

other animal or in humans. No examples were presented of any other drugs targeting μ-opioid receptor for which changes in the UTR of the gene coding for the μ-opioid receptor resulted in altered sensitivity to these drugs.

The state of the prior art

The state of the prior art will be discussed with respect to the following issues:

1) relationship between the changes in the UTR of the gene coding for the μ-opioid receptor in mice and possible implications for other animals and humans,

2) detection of sensitivity to drugs related to the action of the μ-opioid receptor.

With respect to the untranslated region, there is no evidence that altering the length of the untranslated region of the μ-opioid receptor in humans or other animals would confer altered sensitivity to drugs targeting the opioid receptor. Kieffer et al. (Cell. Mol. Neurobiol., vol. 15, pp. 615-635, 1995; cited in the previous office action) teach that human opioid receptors are 85-90% identical to their rodent counterparts in terms of the protein sequence, and that the N-and C-terminal domains display variability across species, and suggest that such differences can lead to changes in pharmacology (page 623, second paragraph). Therefore, the result of changes in the untranslated region of the μ-opioid receptor in mouse cannot be predicted to result in changes in drug response in other animals or humans. Evidence for a difference in untranslated regions of mouse and human receptor genes is provided by Van Spronsen et al. (Eur. J. Biochem., vol. 213, pp. 1117-1124; cited in the previous office action), who teach mouse and human β3-adrenergic receptors (β3-AR), which differ in their 3' untranslated regions (Abstract; page 1118, second paragraph; page 1120, paragraphs 3 and 4; page 1121, second paragraph). The 5' untranslated regions had different promoter structures (page 1120, paragraphs 5 and 6; page 1121, first paragraph). In addition, Van Spronsen et al. suggest that differences responses of rat and mouse β3-ARs mRNAs to stimuli may

be due to differences in promoter responses (page 1122, fifth paragraph). Finally, they suggest that differences in 3' UTRs of alternatively spliced β3-ARs mRNAs may involve destabilization of the mRNAs by agonists (page 1123, the last paragraph).

Xie et al. (Physiol. Genomics, vol. 3, pp. 1-8, 2000; cited in the previous office action) teach two different isozymes of rat intestinal alkaline phospatase (IAP) gene, which differ in their 5' untranslated regions, and the translated proteins respond differently to oleic acid (Abstract; Fig. 5). Xie et al. caution that interpretation of differences in the 5' untranslated region of human AP genes cannot be explained based on differences in the two rat homologues (page 7, third paragraph).

Not all changes in the untranslated region may result in altered sensitivity to a drug. For example, Gscheidel et al. (Polish J. Pharmacol., vol. 52, pp. 27-31, 2000; cited in the previous office action), conducted a study of polymorphisms in the human μ-opioid receptor gene among alcohol-dependent and control subjects. Three 5' UTR polymorphisms were found to have no association with alcohol dependence (Abstract; Table 2; page 30, second paragraph).

Regarding the issue of responses to drugs by μ-opioid receptor-related mechanism, it is well known in clinical practice that response to μ-opioid analgesics, such as morphine, its analogs, and other compounds, varies widely among individuals (Pasternak, The Neuroscientist, vol. 7, pp. 220-231, June 2001; cited in the previous office action). Some individuals respond to a certain drug, while others do not, and there is also incomplete cross-tolerance among many of the mu analgesics (page 221, last paragraph; page 222, first and second paragraphs). Furthermore, morphine and other analgesics, such as the ones shown in Fig. 1 and Table 1 of Pasternak, are not the only substances which interact with the μ-opioid receptors. Other agonists and antagonists interact with the receptors, influencing binding of drugs (page 222, paragraphs 4-6; page 223, first paragraph). Pasternak provides evidence that the CXBK mice, which are a subject of Applicants' experiment

and are insensitive to morphine, exhibit sensitivity to other μ-opioid analgesics, such as M6G, heroin and fentanyl (Fig. 3).

Additional factor which needs consideration in the evaluation of drug sensitivity mediated by a certain type of receptors is interaction between different types of receptors. Mao (Brain Res. Rev., vol. 30, pp. 289-304, 1999; cited in the previous office action) teaches that N-methyl-D-aspartate (NMDA) receptors and opioid receptors can influence each others actions. For example, some NMDA receptor antagonists increase analgesic effects of morphine (page 294, pagraphs 3, 4). As stated by Mao "Interactions between NMDA and opioid receptors could occur in both directions. Thus, any condition which would result in activation of NDMA receptors within the CNS could modulate opioid receptors causing reduced efficacy of opioid analgesia; conversely, repeated treatment with opioids could set up a condition mimicking ongoing nociceptive input through interactions between opioid and NMDA receptors." (page 299, fourth paragraph).

To summarize, due to the fact that the μ-opioid receptor interacts with a variety of different substances, individual variations in opioid drug sensitivity between individuals, and interaction with other receptor systems, such as NMDA receptor, factors causing differences in drug sensitivity are unpredictable, and, as shown by Pasternak, CXBK mice, which do not react to morphine, are still fully responsive to other μ-opioid drugs.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this method to all animals and humans, for all possible polymorphisms in the μ-opioid receptor gene and all drugs targeting the μ-opioid receptor. To start with, all individuals with altered sensitivity to a single drug would have to

be examined, with the consideration of possible cross-talk effects between different types of receptors involved in the drug's metabolism. Since altered sensitivity may mean a very broad range of responses to a drug, which occurs between any two individuals, basically whole populations might need to be screened. Secondly, since all the receptors and most proteins are somewhat involved in metabolism of a drug, either directly or indirectly, basically all mRNAs of all the individuals would have to be examined for differences in their untranslated regions. Such evaluation would also have to include potential splice variants, which may differ in their 5' or 3' UTRs. Finally, all of the above steps would have to be repeated for all other existing drugs. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the reaction of individuals to a given drug depends on numerous known and unknown parameters such as the differences in individual responses to a drug, cross-talk between different receptor systems, a large number of metabolic enzymes involved in drug interactions, differences in enzyme structure due to different gene structure and differences in enzyme-drug interactions due to differences in transcriptional activation of enzymes by the drugs themselves, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to determine how to evaluate these factors to determine the most efficient way of establishing differences in drug sensitivity. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill

level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 8 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 10 depend from cancelled claim 2.

12. No claims are allowed. No references were found teaching or suggesting claims 1, 2 and 7-10, but they are rejected for reasons given above.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
May 4, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER
5/06/04